Biomarkers in PD

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Biomarkers in PD

- Risk factors vs predictors of PD
- Limitations of diagnostic markers
- Measures of progression or response to Rx
- Gaps and future approaches

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Definitions

- Biomarker: A characteristic that is objectively measured and evaluated as an indicator of a normal biological process, pathogenic process, or pharmacologic response to a therapeutic intervention

- Clinical Endpoint: A characteristic or variable that reflects how a patient feels, functions or survives.

- A biomarker intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence."

NIH Definitions Working Group, 2000

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Potential Biomarker Uses in Developing Therapies

Select Populations

Risk for PD: RBD, Smell, Imaging

Diagnosis of PD: clinical signs, imaging

Mechanism of PD: Rep 1, Lrrk 2 mito dysfunction

Prognosis: dementia

Monitor Progression or Rx

Natural History: Urate

Drug Mechanism : Drug exposure – Clinical Pharmacology, Imaging

Response to Intervention: ?

Surrogate Endpoints: XXX

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- More efficient
  - Earlier
  - Objective
  - Reduced noise
  - Easily measured
- Correlates with AND predicts clinical outcome

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Risk for PD

- Age
- Male Gender
- RBD?
- Environmental exposures (MPTP), pesticides, farming, well water
- Constipation
- Decreased smell
- Not smoking or consuming caffeine
- Dietary factors
- Physical inactivity

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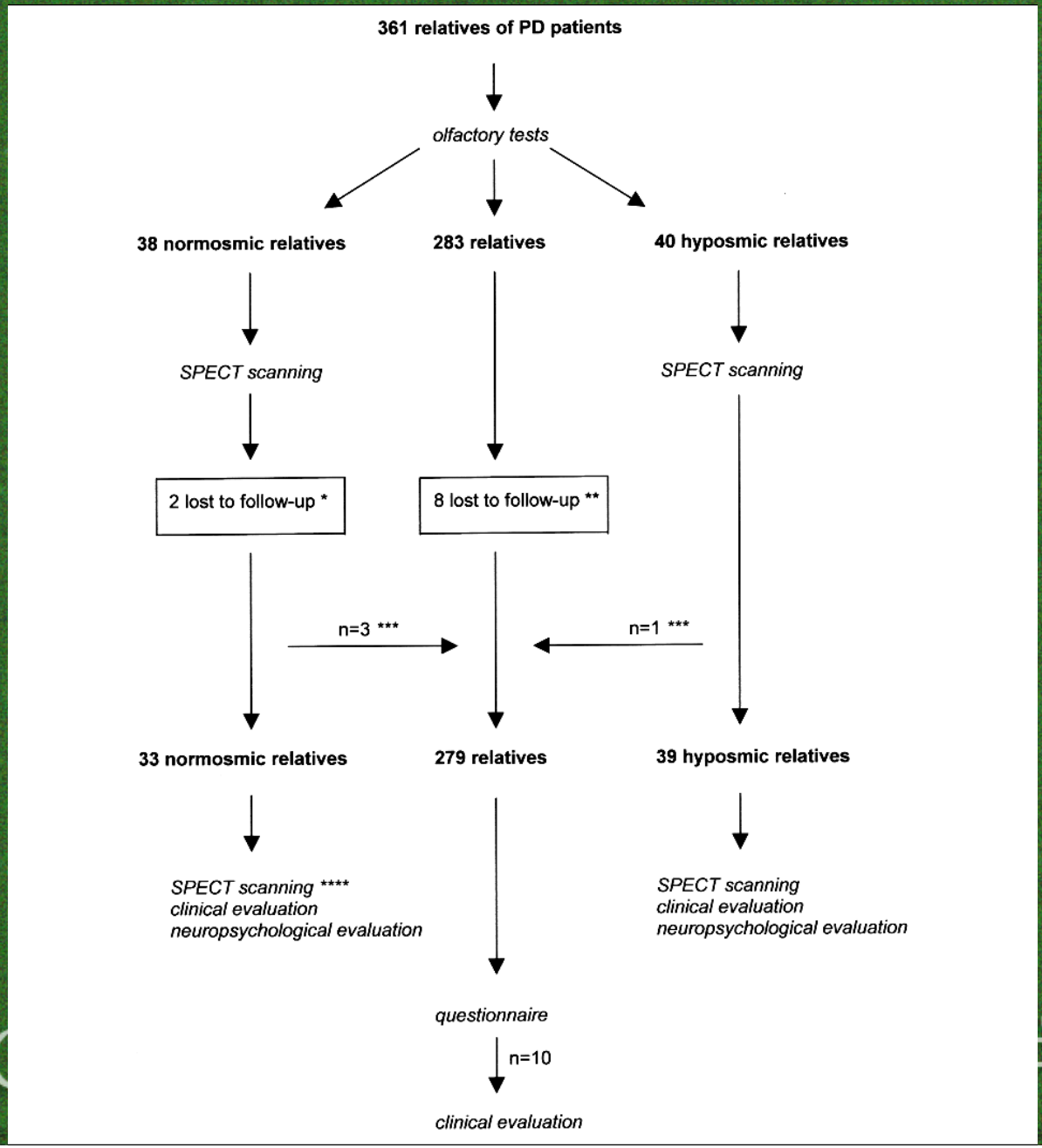
Olfactory Testing and Imaging
Ponsen. Ann Neurol. 2004



Combining Sensitive and Specific Measures

Table 4. Percentage Change from Baseline (mean ± SD) of [^{123}I]β-CIT Binding Ratios over the 2 Year Follow-up Period

Location	Normosmic Relatives, Total (N = 30)	Hyposmic Relatives		
		Total (N = 38)	No Parkinsonism (N = 34)	Parkinsonism (N = 4)
Left striatum	2.46 ± 17.3	−5.61 ± 18.5[a]	−5.59 ± 17.8[a]	−5.75 ± 26.9
Right striatum	2.61 ± 17.0	−6.27 ± 17.7[a]	−6.19 ± 16.5[a]	−6.94 ± 29.0
Left putamen	0.60 ± 19.0	−10.04 ± 15.2[a]	−9.85 ± 15.3[a]	−11.64 ± 16.4
Right putamen	1.99 ± 18.0	−7.03 ± 19.5[a]	−6.46 ± 18.1[a]	−11.91 ± 32.4
Left caudate	2.14 ± 17.5	−3.81 ± 20.3	−3.76 ± 19.7	−4.24 ± 29.2
Right caudate	2.84 ± 18.8	−5.94 ± 19.4[a]	−6.57 ± 18.8[a]	−0.59 ± 26.5

Linear regression analysis using absolute [^{123}I]β-CIT binding ratios (Table 3) was used to analyze group differences.

[a]Significantly different from normosmic group ($p < 0.05$)

Ponsen. Ann Neurol. 2004

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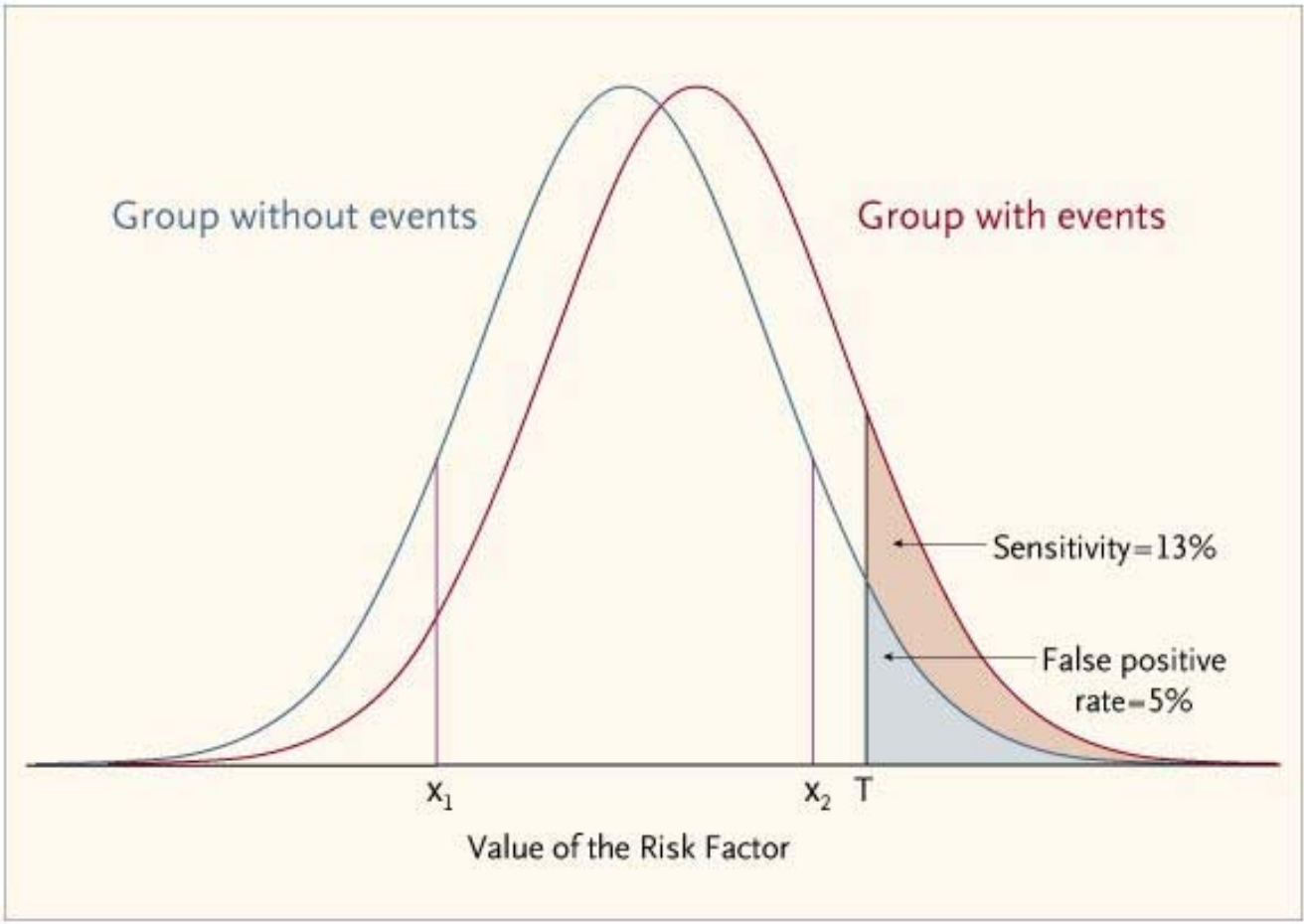
From Risk Factor to Prognosis



Ware J. N Engl J Med 2006;355:2615-2617

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Traditional Emphasis: Diagnosis

- Clinical Signs
  - Early falls, early autonomic
  - Olfaction
  - Levodopa/apomorphine challenge
- Imaging: Fdopa PET, DAT tracer with SPECT
- Other markers:
  - Plt mitochondrial complex I activity (Haas, 1995)
  - Measures of oxidative stress (Kikuchi, 2002)
  - 20S proteasome, caspas-3 markers (Blandini 2006)
  - Inc DJ-1 in CSF (Waragai, 2006)
  - Transcriptomics (Scherzer, 2007)
  - α-synuclein assays (El-Agnaf, 2006)

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Diagnostic Applications: Incorporating Physician belief

- Bayes' theorem tells how to update or revise beliefs (prior probability) in light of new evidence

- Olfaction: 77% sens, 85% spec
  - Prior 85%: posterior probability=97% for + test, 61% for – test
  - Prior 50%: posterior probability=84% for + test, 21% for – test

- RTI: Prior 85%
  - sens 95%, spec 50%: posterior probability=91% for +, 36% for -
  - sens 100%, spec 50%: posterior probability=92% for +, 0 for -
  - Sens 95%, spec 75%: posterior probability=96% for + , 27% for -

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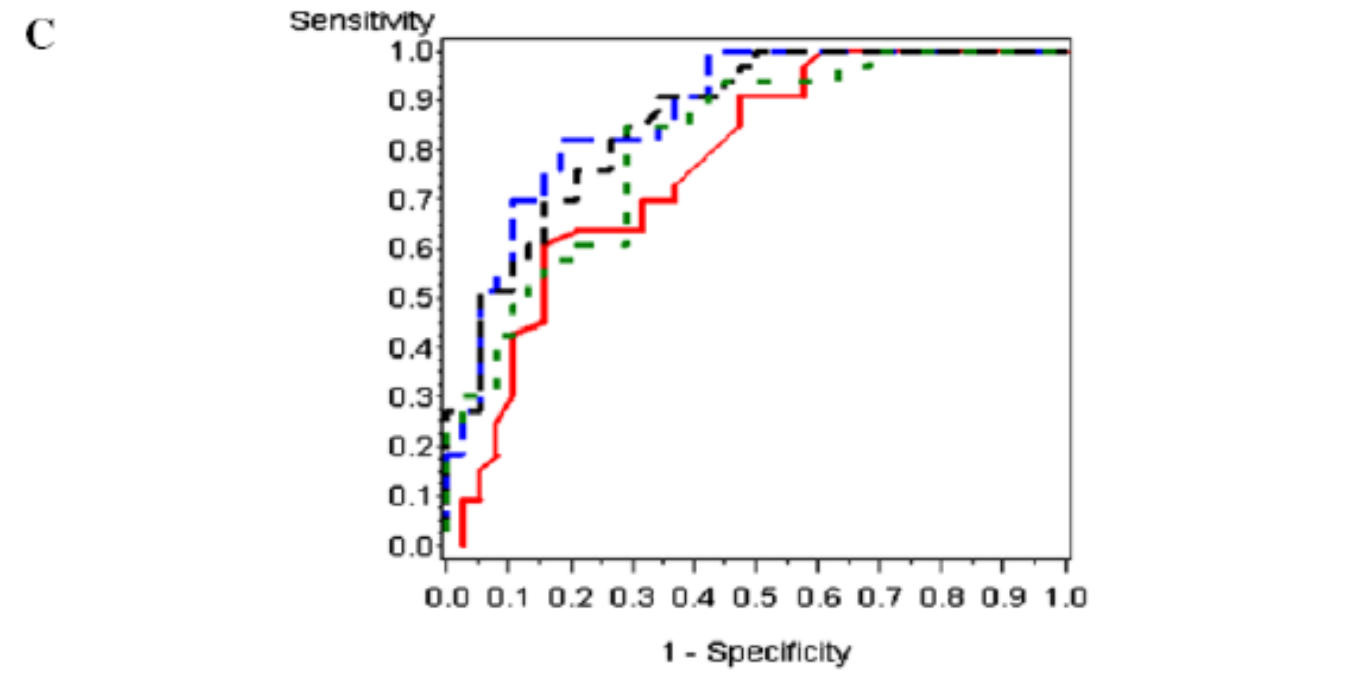
CSF Synuclein



Tokuda T. 2006

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Stages of Marker Development

Type 0: Natural History Marker

Type 1: Biological Activity Marker

Type 2: Marker of Therapeutic Efficacy
"Surrogate Endpoint"

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AChE Inhibition in AD with Donepezil measured with [11 C]PMP and PET

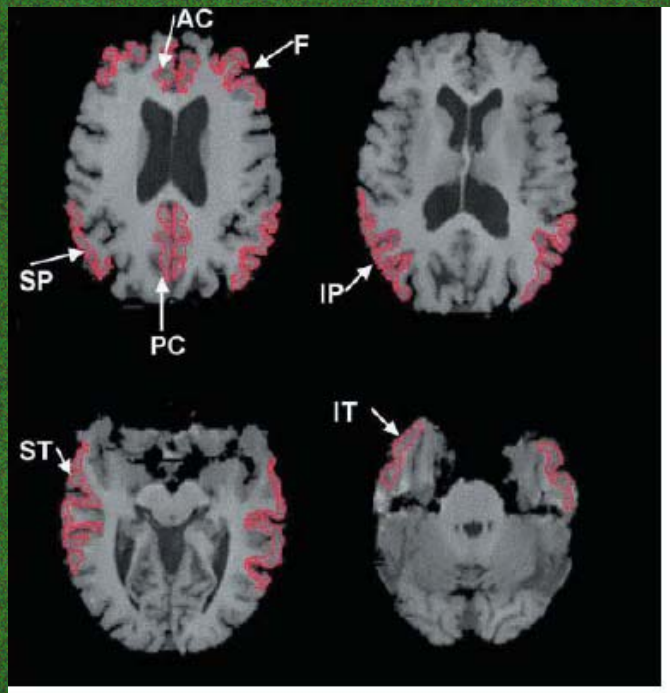

Figure 1 Examples of regions of interest are shown on spoiled gradient recall magnetic resonance images. AC, anterior cingulate; F, dorsolateral prefrontal cortex; IT inferior lateral temporal; IP, inferior lateral parietal; SP, superior lateral parietal; ST, superior lateral temporal.

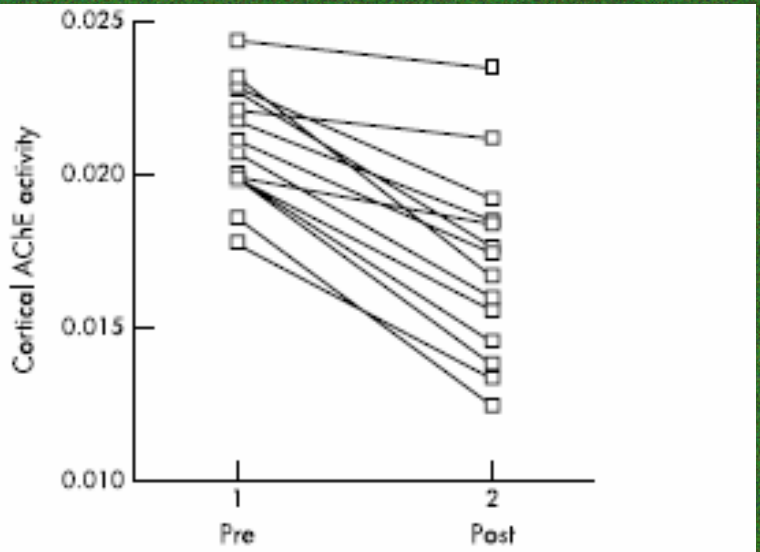

Figure 2 Cortical AChE activity before and at 12 weeks of donepezil treatment in subjects with Alzheimer's disease.

Bohnen, JNNP 2005

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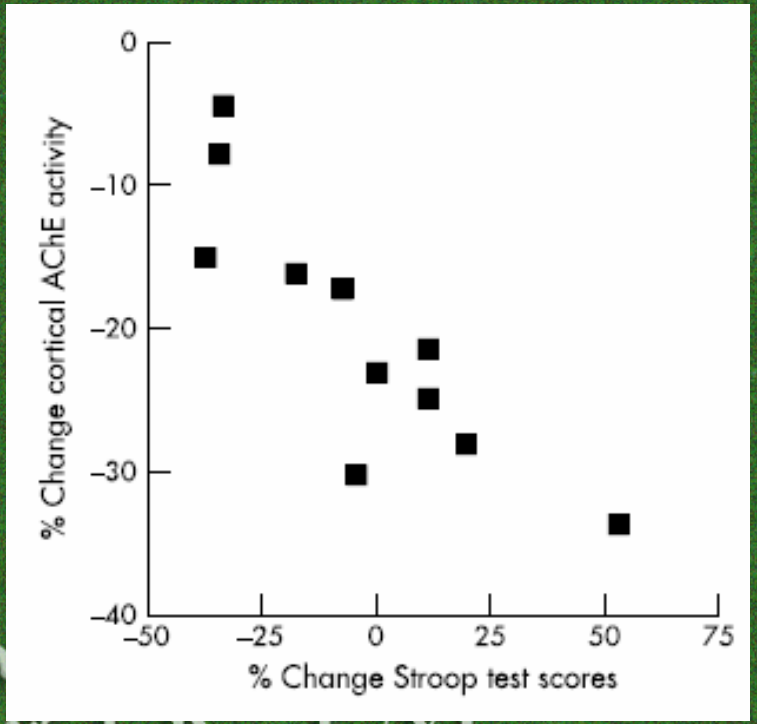
Table 2 Cognitive test scores (mean (SD)) prior to and during 12 weeks of donepezil therapy

	Baseline	12 weeks	% Change	Wilcoxon's signed rank test
MMSE	22.6 (4.3)	23.5 (3.4)	4.0 (16.4)	S=11.5, NS
CVLT-STM	2.0 (2.4)	2.5 (2.3)	25.0 (108.1)	S=5, NS
CVLT-LTM	2.1 (2.5)	2.9 (3.7)	38.1 (124.5)	S=8.5, NS
TMT B (seconds)	215.9 (82.9)	227.5 (80.00)	5.4 (32.6)	S=11.5, NS
Stroop Interference	15.9 (6.0)	15.5 (5.7)	−2.5 (27.1)	S=−8, NS
COWA	28.8 (13.4)	30.3 (10.4)	5.2 (42.2)	S=5, NS

Wilcoxon's signed rank test S values with significance levels are presented.
Attention and executive functions (Stroop Color Word interference test and Trail Making Test, TMT B).
Word fluency (Controlled Oral Word Association, COWA).
CVLT, California Verbal Learning Test; MMSE, Mini-Mental State Examination; S/LTM short/long term memory.



Stroop Color Word Interference
$R^2=0.59$

Trail Making Part B
$R^2=0.79$

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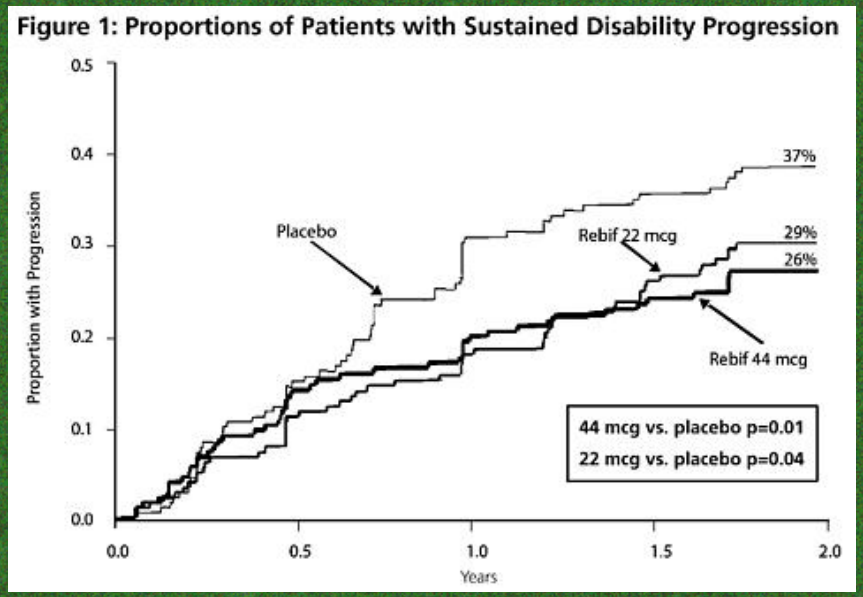
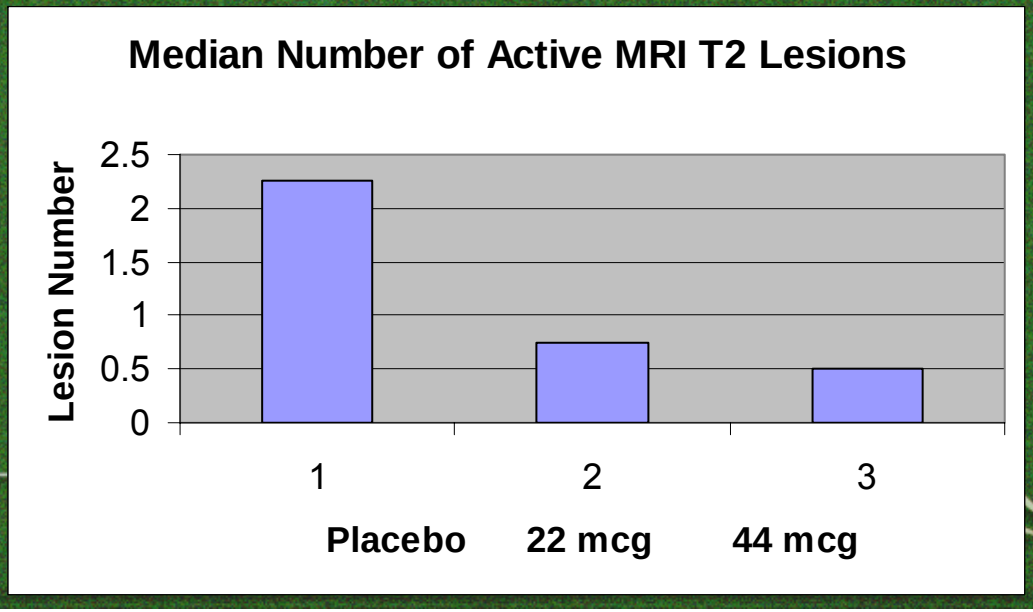
Interferon beta-1a in Multiple Sclerosis: Delaying Accumulation of Disability





Limitations of Approaches

- Risk factors may be difficult to convert to prognostic markers
- Focus on diagnosis: common features of neurodegenerative diseases may make this problematic
- Design Issues
  - Cross sectional designs
  - Small, convenience samples
  - Spectrum bias
  - Little replication or reliability testing
  - Analysis often as sole predictor
- Used alone: multiple markers

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Future Approach: Comprehensive Markers Programs

- Large cohorts available for study
- Allow for:
  - Spectrum of patients
  - Longitudinal eval progression and prognosis
  - Training set with validation
  - Testing multiple markers
  - Reliability (inter rater) testing
  - Storage of samples for new markers
- PostCEPT and PROBE

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Future Approaches

- Surrogate of PD progression (type II) may be far off
- Focus on markers on type 0 and I (drug activity/pharmacology) markers
- Will provide information about mechanism

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